

MAR 24 2005

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
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1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 23.Mar.05	3. REPORT TYPE AND DATES COVERED MAJOR REPORT		
4. TITLE AND SUBTITLE RING-CLOSING METATHESIS OF MACROCYCLIC COMPOUNDS AND CROSS-METATHESIS OF ALLYL ESTERS OF AMINO ACIDS LEADING TO PEPTIDOMIMETICS		5. FUNDING NUMBERS		
6. AUTHOR(S) CAPT LOW TAMMY K				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF FLORIDA		8. PERFORMING ORGANIZATION REPORT NUMBER  CI04-1008		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433		10. SPONSORING/MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1		12b. DISTRIBUTION CODE		
13. ABSTRACT (Maximum 200 words)				
14. SUBJECT TERMS			15. NUMBER OF PAGES 3	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	


TOPIC: Combinatorial, Parallel, and Solid Phase Chemistry

TITLE: Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Esters of Amino Acids Leading to Peptidomimetics

AUTHORS: Tammy K.C. Low and Eric Enholm


The preparation of a dynamic combinatorial library of peptides using the cross-metathesis of allyl esters of amino acids was examined in a model study. This preliminary investigation employed Grubbs' second generation catalyst for the ring-closing metathesis of unique macrocyclic systems. An N-allyl lactam function, that was part of the large ring, was reacted with allyl esters of amino acids in a cross-metathesis coupling. The reversibility of the reaction, the modified amino acids, and the dynamic biomimetic aspects were all of interest in this study on new types of cyclic peptidomimetics.

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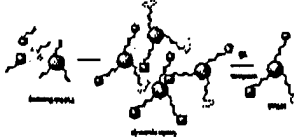
## Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetics

TAMMY K.C. LOW and ERIC J. ENHOLM  
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI, GAINESVILLE, MO 65211



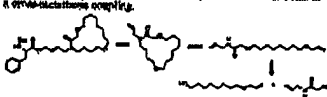
### INTRODUCTION

Ring-closing and cross-metathesis reactions are important tools in organic synthesis. The reversibility of cross-metathesis makes it ideal for use in dynamic combinatorial chemistry. In particular, we are interested in generating a library of new cyclic peptidomimetics. The reversibility of the reaction, the resulting amino acids, and the dynamic bioactive aspects are all of interest in this study.

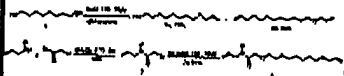


### MODEL STUDY

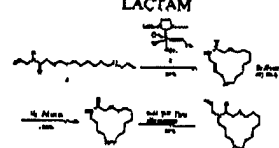
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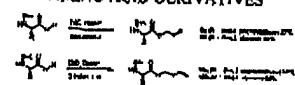
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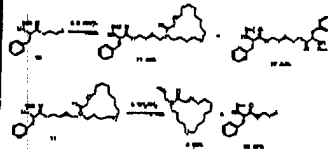


### AMINO ACID DERIVATIVES



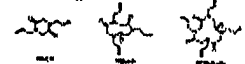
1. Grubbs, R. H. *J. Am. Chem. Soc.* 1995, 117, 2571.  
 2. Grubbs, R. H.; Ziegler, H. *J. Am. Chem. Soc.* 1998, 120, 1214.  
 3. Grubbs, R. H. *J. Org. Chem.* 1998, 63, 1001.

### CROSS-METATHESIS



### CURRENT EFFORTS

The Model Study has demonstrated the reversibility of the cross-metathesis reaction of an allyl ester of amino acid with N-allyl lactam, a key toward creating a dynamic library. Based on these studies, we are synthesizing N-allyl lactams with various number of "links" (three, trimer, and tetramer). In the future studies, a small library of cyclic peptidomimetics was generated. Various templates are now being examined to shift the equilibrium where only one major component of the library is formed. Results of these studies will be released in the near future.



### ACKNOWLEDGEMENTS

Grubbs Group Members:  
 Joel Hirsinger, Sophie Klein, Ryan Martin, and Katelyn Mendel

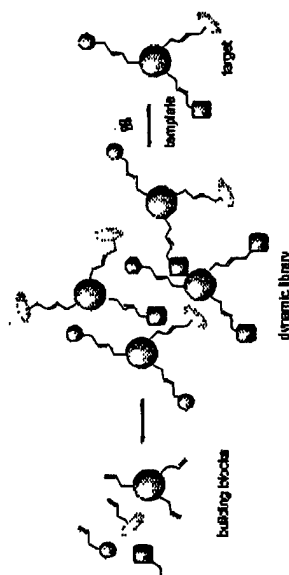


# Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetic

TAMMY K.C. LOW and ERIC J. ENHOLM

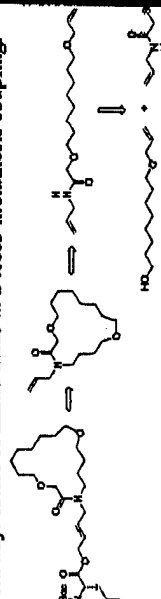
## INTRODUCTION

Ring-closing and cross-metathesis reactions are important tools in organic synthesis<sup>1</sup>. The reversibility of cross-metathesis makes it ideal for use in dynamic combinatorial chemistry. In particular, we are interested in generating a library of new cyclic peptidomimetics. The reversibility of the reaction, the modified amino acids, and the dynamic biomimetic aspects are all of interest in this study.

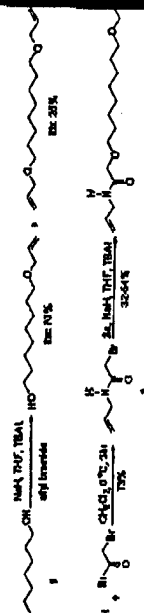


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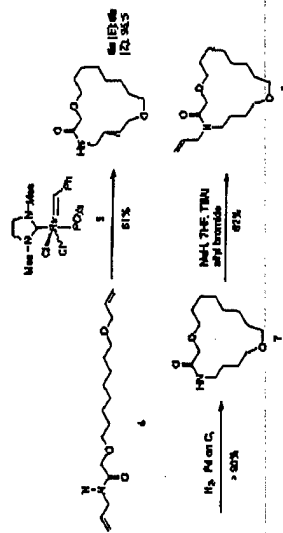
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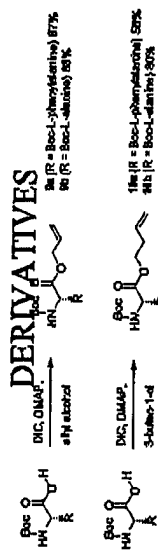


## LACTAM



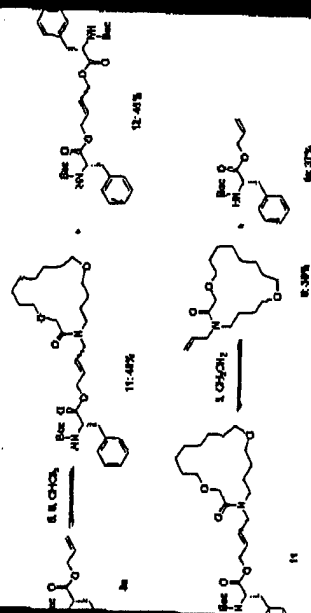
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### DERIVATIVES



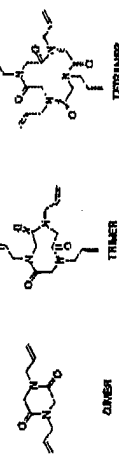
<sup>1</sup>Blackwell H. E. et al. *J. A. Chem. Soc.* 2000, 122, 58-71.  
<sup>2</sup>Reichwein, J. F.; Lickamp, B. M. *J. Eur. J. Org. Chem.* 2000, 12, 2335-2344.  
<sup>3</sup>Smith, H. et al. *Macromolecules* 2004, 37, 10215-10224.

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Enholt Group Members:  
 Jed Hastings, Sophie Klein, Ryan Martin, and Kalyan Mandal

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